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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4/15/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 2, 3, 5, 7 + 9-27 are pending in the application.
   Of the above, claims 9-21 are withdrawn from consideration.
2. ☒ Claims 1, 4, 6 + 8 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 2, 3, 5, 7 + 22-27 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 2, 3, 5, 7, + 9-29 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 2, 3, 5, 7, and 22-27, drawn to an extracellular domain of HER2 and vaccines, classified in Class 530 and 424, subclasses 350 and 88, respectively, for example.

II. Claims 9-21, drawn to DNA and a method of expression, classified in Class 536, subclass 23.5, for example.

16. The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case the polypeptide of group I can be made by recombinant methodology, by cleavage of the natural protein or by chemical synthesis. In addition, Inventions I and II are patentably distinct because the DNA and proteins are physically, chemically and biologically distinct and are capable of separate manufacture, use and sale. A search of the relevant patent and technical literature would require a search in databases devoted exclusively to nucleic acid sequences for the DNA and amino acid sequences for the proteins.

17. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification restriction for examination purposes as indicated is proper.

18. During a telephone conversation between Examiner Moser and Janet Hasek on 7 September 1993 a provisional election was made with traverse to prosecute the invention of Group I, claims 2, 3, 5, 7, and 22-27. Affirmation of this election must be made by applicant in responding to this Office action. Claims 9-21 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

19. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

20. Claims 2 and 24 are rejected under 35 U.S.C. § 101 because the

claimed invention is directed to nonstatutory subject matter.

The cited Langton et al. and Lin et al. references are evidence that the extracellular domain of HER2 (p185, c-erbB-2) is naturally shed in soluble form from tumors into serum (see the abstract of each reference, for example). In order to be shed in soluble form the protein must be free of the transmembrane and intracellular portions of the HER2 molecule. Accordingly, the claimed extracellular HER2 protein has the same characteristics and utility as the naturally occurring polypeptide shed from tumor cells in vivo. It is noted that claim 24 is directed to a vaccine however, there are no limitations in the claim which distinguish it from the natural product.

17. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 2, 3, 5, 7, and 22-27 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility.

The claimed invention is alleged to be useful for further research, such as for purification of the putative receptor ligand, as well and in potential therapeutic applications (p. 21 of the

specification). The evidence of record does not establish that the invention is useful outside of a fundamental research setting or for further experimentation. Utility for further experimental research does not establish a patentable utility according to § 101. Utility must be definite and in currently available form, not merely for further investigation or research. MPEP 608.01(p), Brenner v. Manson 148 USPQ 689.

The specification fails to establish the utility of the claimed extracellular domain and vaccines in any method of treatment, such as treatment of tumors, which requires therapeutic use in vivo and those skilled in the art would question the objective truth of the statement of utility as a therapeutic agent or vaccine. The assertion of utility is based on pure speculation and there is no in vitro or in vivo evidence of record in support of therapeutic utility. While in vitro results are useful in screening for potentially therapeutic molecules, one cannot simply extrapolate this success to an in vivo system and there are no working examples which demonstrate that the claimed compositions will be effective *in vivo* as an effective tumor therapy. Successful use of the claimed invention in vivo is dependent on adequate concentrations of the protein remaining biologically active for a sufficient time to have a significant biological effect. Numerous variable parameters contribute in determining the degree of success achieved in experimental and clinical protocols. For example, properties of the therapeutic agent such as,

biological stability, half-life or rate of clearance from the blood are variable parameters which can present obstacles to successful therapeutic use. The extracellular domain or its ligand may be inactivated in vivo before producing a sufficient effect, e.g. such as proteolytic degradation, immunological inactivation or due to an inherently short half life of the protein (e.g. rapid deactivation/excretion by the kidney) and there are no tests of record which sufficiently duplicate conditions which occur in vivo. In addition, the protein may otherwise not reach the desired target area because, for example,

(a) the protein may not be able to penetrate tissues and/or cell membranes where its activity could be exerted,

(b) the protein may have poor bioavailability (e.g. may be adsorbed or absorbed by fluids, cells and tissues where the protein has no effect),

(c) circulation to or in the target area may be insufficient to carry the drug; or

(d) A large enough effective local concentration may not be capable of being established even with administration of excess amounts, particularly as such relates to ensuring that adverse side effects do not occur that would prohibit use of such compound in therapy.

See M.P.E.P. 608.01(P) and Ex parte Aggarwal, 23 USPQ2d 1334 1337 1338 (BPAI 1992). Filing of evidence of successful use of the

claimed extracellular protein or vaccine using model systems, such as animal models, which are accepted in the art or other models which are reasonably predictive of successful tumor therapy would overcome this rejection.

19. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to teach how to make and use the invention ie. failing to provide an enabling disclosure.

This objection is set forth for essentially the reasons discussed above. "If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112." In re Ziegler, 26 USPQ2d 1601. Evidence of utility is required.

The evidence of utility must be commensurate in scope with the claims with respect to the extracellular portion of the HER2 molecule. Claim 1, for example is directed to any portion of the HER2 extracellular domain and page 3 of the specification suggests

that the portion may be as small as 9 amino acid residues. The scope of the claims is not commensurate with the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

The specification does not support the broad scope of the claims which encompass all fragments of the HER2 extracellular domain because the specification does **not** disclose the following: (A) the general tolerance to modification and extent of such tolerance; (B) specific positions and regions throughout the protein's sequence which can be predictably modified and which regions are critical for biological activity; (C) what fragments, if any, can be made which have the desired biological activity of the intact protein; and (D) the specification provides insufficient

guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any portion of the HER2 extracellular domain. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the portions of the extracellular domain which retain the desired anti-tumor activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986); Amgen, Inc. v. Chugai Phamaceutical Co, Ltd. 927 F.2d 1200, 18 USPQ2d 1016, (Fed. Cir. 1991) at 18 USPQ2d 1026-1027; Ex parte Maizel, 27 USPQ2d 1662 (BPAI, 1993).

Claims 2, 3, 5, 7, and 22-27 are rejected under and 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

20. Claim 7 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 7 it is not clear what is encompassed by a peptide

having immunogenic properties. Clarification is required.

21. Claims 22 and 24 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 22 and 24, while directed to vaccines, fail to recite any limitation which distinguish them from claims 2 or 26.

22. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the

obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

23. Claims 2, 3, 5, 7, and 22-27 are rejected under 35 U.S.C. § 103 as being unpatentable over Yamamoto et al. (AJ) or Coussens et al. (AL) each in view of Weber et al., Dull et al. or Dower et al.

Each of Yamamoto et al. and Coussens et al. teach the complete nucleotide and amino acid sequences for the HER2 (same as c-erbB-2) tyrosine kinase receptor (see Fig. 3 of Coussens and Fig. 2 of Yamamoto). Importantly, each of the references further delineate that region of the receptor which constitutes the extracellular domain (see 1137, first full paragraph of Coussens and Fig. 3B of Yamamoto). These references do not teach production of a protein containing the extracellular domain without the transmembrane and cytoplasmic domains. However, each of the secondary references teach the advantages of obtaining soluble extracellular domains of receptor proteins. For example, Weber et al. teach recombinant preparation of two soluble forms of the IL-2 receptor lacking the transmembrane and cytoplasmic domains (see the abstract and p. 56). Weber et al. teach that soluble receptors have practical applications in drug screening assays and receptor affinity

purification of the ligand. Dower et al. similarly teach the means for preparing a recombinant IL-1 receptor wherein the transmembrane region and intracellular domains have been deleted (col. 14, lines 20-26) as well as a composition comprising a receptor and adjuvant for making antibodies (Example 7). Dull et al. teach hybrid receptors comprising a receptor ligand binding domain and a reporter polypeptide, which would inherently have "immunogenic properties," and assays for identifying biologically active ligands or their antagonists or agonists (see the entire document, especially cols. 1-2). The HER2 receptor is typical of cell surface receptors in that the ligand binding domain resides in the extracellular region (p. 1133, third column of Coussens). At the time this invention was made it would have been prima facie obvious to a person having ordinary skill in this art to prepare a soluble, extracellular domain of the HER2 receptor, as taught by Coussens et al. and Yamamoto et al. One would have been so motivated so that it may be used for practical applications such as drug screening assays, receptor affinity purification of the ligand, or to prepare hybrid receptors comprising a receptor ligand binding domain to be used in assays for identifying biologically active ligands of the c-erbB-2 receptor or their antagonists or agonists.

24. Claims 2, 3, 5, 7, and 22-27 are rejected under 35 U.S.C. § 103 as being unpatentable over Yamamoto et al. (AJ) or Coussens et al. (AL) each in view of Bernards et al. (AR) and further in

view of Maddon et al., Hudziak et al (AO), or Masuko et al.

Each of Yamamoto et al. and Coussens et al. teach the complete nucleotide and amino acid sequences for the HER2 tyrosine kinase receptor (see Fig. 3 of Coussens and Fig. 2 of Yamamoto). Importantly, each of the references further delineate that region of the receptor which constitutes the extracellular domain (see 1137, first full paragraph of Coussens and Fig. 3B of Yamamoto). These references do not teach production of a protein containing the extracellular domain without the transmembrane and cytoplasmic domains. However, Bernard et al. teach expression of the rat neu protein, which is the rat homolog of the human HER2, in a form lacking the majority of the cytoplasmic domain (p. 6854) and that the protein protected animals against tumor cell challenge (Abstract). The protein of Bernards et al. is not soluble, ie lacking the transmembrane region. However, Maddon et al. teach that a soluble receptor may be used as a therapeutic agent or to raise specific antibodies against the soluble portion of the receptor which may be useful for therapy (col. 3, lines 6-20). Each of Hudziak et al. and Masuko et al. teach the preparation of monoclonal antibodies specifically directed against the extracellular domain of HER2. Hudziak et al. teach that such antibodies may be useful for treatment of human neoplasias (see 1171, last sentence). Masuko et al. teach that antibodies against HER2 (same as c-erbB-2) will be useful to characterize the c-erbB-2 gene product, for diagnosis and for therapy of certain human tumors

(see the first paragraph). At the time this invention was made it would have been prima facie obvious to a person having ordinary skill in this art to prepare a soluble, extracellular domain of the HER2 receptor, as taught by Coussens et al. and Yamamoto et al. One would have been so motivated so that it may be used as a vaccine as taught by Bernards et al. or to prepare monoclonal antibodies useful for diagnosis or therapy of human tumors, as taught by Hudziak or Masuko. One would have reasonably expected a recombinant, extracellular domain lacking the transmembrane and cytoplasmic regions to have such uses in view of Maddon et al. which teaches that a soluble receptor may be used as a therapeutic agent or to raise specific antibodies against the soluble portion of the receptor which may be useful for therapy.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to R. Keith Baker whose telephone number is (703) 308-2958.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

R. Keith Baker

KEITH BAKER
PATENT EXAMINER
GROUP 1800

9/23/93